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WEINGARTEN, SCHURGIN, GAGNEBIN & LEBOVICI LLP
TEN POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER	
WOODWARD, CHERIE MICHELLE	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,687	KAZLAUSKAS ET AL.	
	Examiner	Art Unit	
	CHERIE M. WOODWARD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *12-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/18/2006,10/2/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-11) in the reply filed on 5/21/2008 is acknowledged. The traversal is on the grounds that Wittenmayer et al., teaches that low profilin-1 levels are related to the tumorgenic state of the tested cells (Remarks, page 7). Applicant argues that the instantly claimed method is directed to increased or elevated profilin-1 levels as diagnostic of a disease or a condition associated with endothelial cell dysfunction (Remarks, page 7). Applicant amended claim 1 to clarify this distinction. This is not found persuasive because although profilin-1 normally acts as a tumor suppressor and low levels of expression of profilin-1 have been found in some tumor cells, Wittenmayer et al., teach that elevation of overall profilin-1 levels in human breast carcinoma cells (endothelial cells) were capable of reverting the tumorgenic state (p. 1606, column 2, second paragraph). Claim 1, as amended, in the "providing" step recites that a subject only need be "thought to be at risk" or (in the alternative) suffering from a disease or (in the alternative) condition associated with endothelial cell dysfunction. The alternative readings of the "providing" step do not require the subject to have an actual or diagnosed disease. In its broadest reasonable interpretation, the claim also reads on determining the level of profilin-1 in a patient that is healthy or has elevated levels of profilin-1 in relation to a patient with a tumor, for example. Additionally, the "relating" step recites that an elevated level of profilin-1 relates to a disease or (in the alternative) a condition of the subject. In the broadest reasonable interpretation, the "reciting" step can be read to correlate an elevated level of profilin-1 with a condition of being healthy or a condition of not having a tumor. The alternative readings of claim 1, as amended, still bring the claim within the anticipatory teachings of Wittenmayer et al.

The requirement is still deemed proper and is therefore made FINAL.

Formal Matters

2. Claims 1-27 are pending. Claims 12-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction/election requirement in the reply filed on 5/21/2008. Claims 1-11 are under examination.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 9/18/2006 and 10/2/2006 have been considered by the examiner. Signed copies are attached.

Drawings

4. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(4) because reference character "Figure 3" has been used to designate three separate drawings. Compare Figure 8 in the inventor's after-filed publication, Romeo et al., (FASEB J. 2004 Apr;18(6):725-7, Epub 20 February 2004 (cited on Applicant's IDS of 9/18/2006). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

5. The disclosure is objected to because of the following informalities: the brief description of the drawings should be updated to correspond with the corrected Figure 3 subparts. Appropriate correction is required.

6. The listing of references in the specification is not a proper information disclosure statement (see pages 22-24). 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, and 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the level of profilin-1 in a tissue, including a vascular sample, an and a retinal tissue sample, does not reasonably provide enablement for determining the level of profilin-1 in a serum or plasma sample, such that the level of profilin-1 in the blood sample reasonably correlates with a suspected or actual disease or condition or state thereof in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is drawn to a method of determining the state of a disease or condition associated with endothelial cell dysfunction by measuring the level of profilin-1 in a subject at a site in the subject. Claim 1 is generic with regard to the site of the associated with the vascular sample. Claim 6, is generic with regard to the vascular sample. Claims 7 and 8 recite that the vascular sample is serum and plasma, respectively.

Wittenmayer et al., teach a method of determining a disease state associated with endothelial cell dysfunction (tumor growth) *in vivo* in mice by determining the levels of profilin-1 (PFN-1) and relating elevated levels of PFN-1 to the state of the disease (tumor) (p. 1606, column 2, second paragraph; Figures 6 and 7) (compare instant claim1). Although it is known that profilin-1 normally acts as a tumor suppressor and low levels of expression of profilin-1 have been found in some tumor cells, Wittenmayer et al., teach that elevation of overall profilin-1 levels in human breast carcinoma cells (endothelial cells) were capable of reverting the tumorgenic state (p. 1606, column 2, second paragraph). Wittenmayer et al., also teach determination of levels of profilin-1 in tissue samples, which contain vascular samples

(Figures 6 and 7; especially the description of Figure 6). Wittenmayer et al., explains that "PFN1 expression in most human tissues is within a narrow range, not exceeding a three-fold difference from the mean. Exceptions from this rule are spleen and tissues with a relatively high expression of other profiling isoforms, i.e. brain and testis" (page 1606, column 1, last paragraph to column 2, first paragraph). In light of this prior art teaching, one of ordinary skill in the art would be aware that different tissues contain different levels of PFN1, with most tissues not exceeding a three-fold difference from the mean in profilin-1 expression. One of ordinary skill in the art would not be able to determine whether a subject is suffering from any particular disease or condition by measuring the amount of profilin-1 in plasma or serum because plasma and serum are systemic in nature and circulate throughout the body.

Page 8, third paragraph, of the specification teaches that circulating levels of profilin-1 and anti-profilin-1 antibodies as specific markers for human DVD (diabetic vascular disease). However, there are no working examples or other data showing that circulating levels of profilin-1 are specific for any disease. Although working examples are not required, they are helpful in determining whether Applicant has adequately taught how to make or use the invention, as claimed.

The specification teaches *in vivo* methods of determining profilin-1 expression on the surface of endothelial cells in the aorta, femoral, and carotid arteries of a subject, exemplified by the LDL receptor knockout (Ldlr) mouse (page 7, last paragraph). Example 1 teaches the determination of expression of profilin-1 in diabetic aortic tissue samples (page 17). Example 4 teaches determination of expression of profilin-1 in aortic sinus atherosclerotic plaques and disease-free adjacent areas (page 20). There is insufficient guidance and data in the specification to support Applicant's claims of determining the level of profilin-1 at a vascular site encompassing serum or plasma. Without additional guidance, one of ordinary skill in the art would not be able to make or use the claimed invention to determine the level of soluble profilin-1 in the blood (serum/plasma) such that it could be correlated with a state of disease or condition of the subject. Without additional guidance, the skilled artisan would not be able to determine where the soluble profilin-1 came from or what tissue it originated from, in order to determine whether the detected levels were associated with a vascular condition or any other type of condition or disease.

Due to the large quantity of experimentation necessary to determine a elevated level of profilin-1 expression in serum or plasma from a subject and correlate the same with a suspected or actual disease or condition or state thereof, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that different tissues express different levels of profilin-1, undue

experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

9. Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the level of profilin-1 in a tissue sample from an LDL receptor knockout (Ldlr) mouse, a rat, and ApoE null mice, and correlating an elevation in profilin-1 with a suspected or actual disease or condition, but does not reasonably provide enablement for determining the level of profilin-1 in a sample from a generic subject (i.e. non-rat/mouse/murine species) and correlating an elevation in profilin-1 with a generic suspected or actual disease or condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is drawn to a method of determining the state of a disease or condition associated with endothelial cell dysfunction by measuring the level of profilin-1 in a generic subject having or suspected of having a generic disease or condition. Claims 1 and 2 are generic with regard to the genus/species of the subject. Claims 1 and 2 are also generic with regard to the disease or condition. Claim 2 is generic with regard to the state of the generic disease or condition.

Wittenmayer et al., teach a method of determining a disease state associated with endothelial cell dysfunction (tumor growth) *in vivo* in mice by determining the levels of profilin-1 (PFN-1) and relating elevated levels of PFN-1 to the state of the disease (tumor) (p. 1606, column 2, second paragraph; Figures 6 and 7) (compare instant claim1). Although it is known that profilin-1 normally acts as a tumor suppressor and low levels of expression of profilin-1 have been found in some tumor cells, Wittenmayer et al., teach that elevation of overall profilin-1 levels in human breast carcinoma cells (endothelial cells) were capable of reverting the tumorgenic state (p. 1606, column 2, second paragraph). Wittenmayer et al., also teach determination of levels of profilin-1 in tissue samples (Figures 6 and 7; especially the description of Figure 6). Wittenmayer et al., explains that "PFN1 expression in most human tissues is within a narrow range, not exceeding a three-fold difference from the mean. Exceptions from this rule are

spleen and tissues with a relatively high expression of other profiling isoforms, i.e. brain and testis" (page 1606, column 1, last paragraph to column 2, first paragraph). See also, Su et al., (PNAS USA. 2002. 99;4465-4470; full-length paper and abstract showing mouse and human comparison data at hyperlink: expression.gnf.org; copies of the human PFN1 and mouse PFN1 tissue expression patterns and levels from the referenced hyperlink database are attached for ease of reference).

Based on the prior art teachings and information available in publicly accessible databases prior to the time of the instant invention, one of ordinary skill in the art would be aware that different tissues of different species contain different levels of profilin-1 (PFN1) (see Su et al., *supra*). In humans, Wittenmayer et al., and the data from Su et al., demonstrate that most tissues do not exceeding a three-fold difference from the mean in profilin-1 expression. However, as can be seen from the difference in expression levels of PFN1 in various tissues, mice and humans differ substantially. Moreover, based on the claims, as written, and the data from Wittenmayer et al., that "PFN1 expression in most human tissues is within a narrow range, not exceeding a three-fold difference from the mean," one of ordinary skill in the art would not be able to determine which base level of PFN1 expression to consider relevant in determining an "elevated" level at any given site in a generic species, such that the skilled artisan would be able to correlate the data with any suspected or actual disease or condition, or state thereof.

It is noted that the specification teaches that the exemplary LDL receptor knockout (Ldlr) mouse is understood to be a valid model for human atherosclerotic disease (page 7, last sentence to page 8, first sentence). This may be true, but the Ldlr mouse model is not necessarily a valid model for human profilin-1 expression. Absent evidence to the contrary, it is more likely that the Ldlr mouse model has a typical mouse profilin-1 profile that cannot be accurately or precisely used to compare measurements of human profilin-1. Simply put, Applicant's examples appear to compare apples to oranges in terms of whether an elevation in profilin-1 in any generic species may be reasonably correlated with a suspected or actual disease or condition or state thereof. The data by Su et al., support the examiner's reasoning and show large fold differences in normal profilin-1 expression in human and mouse tissues.

There are no working examples or other data in the specification showing levels of profilin-1 in any human tissue, vascular sample, blood, or serum, such that elevated levels are shown to correlate with any suspected or actual human disease or condition or state thereof. Although working examples are not required, they are helpful in determining whether Applicant has adequately taught how to make or use the invention, as claimed. Additionally, the teaching of Wittenmeyer et al., show the profilin-1 levels in humans to be highly regulated and tightly controlled on a tissue-by-tissue basis (page 1606, column 1, last paragraph to column 2, first paragraph).

There is insufficient guidance and data in the specification to support Applicant's claims drawn to generic species and correlating an elevation in profilin-1 with a generic suspected or actual disease or condition. Without additional guidance, one of ordinary skill in the art would not be able to predictably make or use the claimed invention without undue experimentation to determine the level of soluble profilin-1 in the different tissues of different species of subjects, establishing controls or a base-line, and then determining an elevation in profilin-1 levels in any given tissue correlated with a suspected or actual disease or condition or state thereof..

Due to the large quantity of experimentation necessary to determine an elevated level of profilin-1 in a generic sample of a generic species correlate the same with a suspected or actual disease or condition or state thereof in the generic subject, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that different tissues express different levels of profilin-1 in different species, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

10. Claims 1, 3-5, 10, and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the level of profilin-1 in a tissue sample from an LDL receptor knockout (Ldlr) mouse, a rat, and ApoE null mice, and correlating an elevation in profilin-1 with atherosclerosis, does not reasonably provide enablement for determining the level of profilin-1 in a sample of aortic tissue or retinal tissue from a non-rat/mouse/murine species and correlating the elevated level of profilin-1 expression with a vascular condition, a diabetic vascular condition, atherosclerosis, PVD, CVD, or a combination thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is drawn to a method of determining the state of a disease or condition associated with endothelial cell dysfunction by measuring the level of profilin-1 in a generic subject

having or suspected of having a generic disease or condition. Claim 1 is generic with regard to the genus/species of the subject and the suspected or actual disease or condition or state thereof. Claims 3-5 recite more specific disease or conditions. Claims 10 and 11 recite specific types of tissue samples, aortic tissue samples and retinal tissue samples, respectively.

Wittenmayer et al., teach a method of determining a disease state associated with endothelial cell dysfunction (tumor growth) *in vivo* in mice by determining the levels of profilin-1 (PFN-1) and relating elevated levels of PFN-1 to the state of the disease (tumor) (p. 1606, column 2, second paragraph; Figures 6 and 7) (compare instant claim1). Although it is known that profilin-1 normally acts as a tumor suppressor and low levels of expression of profilin-1 have been found in some tumor cells, Wittenmayer et al., teach that elevation of overall profilin-1 levels in human breast carcinoma cells (endothelial cells) were capable of reverting the tumorgenic state (p. 1606, column 2, second paragraph). Wittenmayer et al., also teach determination of levels of profilin-1 in tissue samples (Figures 6 and 7; especially the description of Figure 6). Wittenmayer et al., explains that "PFN1 expression in most human tissues is within a narrow range, not exceeding a three-fold difference from the mean. Exceptions from this rule are spleen and tissues with a relatively high expression of other profiling isoforms, i.e. brain and testis" (page 1606, column 1, last paragraph to column 2, first paragraph). See also, Su et al., (PNAS USA. 2002. 99;4465-4470; full-length paper and abstract showing mouse and human comparison data at hyperlink: expression.gnf.org; copies of the human PFN1 and mouse PFN1 tissue expression patterns and levels from the referenced hyperlink database are attached for ease of reference).

Based on the prior art teachings and information available in publicly accessible databases prior to the time of the instant invention, one of ordinary skill in the art would be aware that different tissues of different species contain different levels of profilin-1 (PFN1) (see Su et al., supra). In humans, Wittenmayer et al., and the data from Su et al., demonstrate that most tissues do not exceeding a three-fold difference from the mean in profilin-1 expression. However, as can be seen from the difference in expression levels of PFN1 in various tissues, mice and humans differ substantially. Moreover, based on the claims, as written, and the data from Wittenmayer et al., that "PFN1 expression in most human tissues is within a narrow range, not exceeding a three-fold difference from the mean," one of ordinary skill in the art would not be able to predictably determine which base level of PFN1 expression to consider relevant in determining an "elevated" level at any given site in a generic species, such that the skilled artisan would be able to correlate the data with a generic suspected or actual disease or condition, or state thereof.

It is noted that the specification teaches that the exemplary LDL receptor knockout (Ldlr) mouse is understood to be a valid model for human atherosclerotic disease (page 7, last sentence to page 8, first sentence). Although this may be true, but the Ldlr mouse model is not necessarily a valid model for human profilin-1 expression. Absent evidence to the contrary, it is more likely that the Ldlr mouse model has a typical mouse profilin-1 profile that cannot be accurately or precisely used to compare measurements of human profilin-1. Simply put, Applicant's examples appear to compare apples to oranges in terms of whether an elevation in profilin-1 in any generic species may be reasonably correlated with a suspected or actual disease or condition or state thereof. The data by Su et al., support the examiner's reasoning and show large fold differences in normal profilin-1 expression in human and mouse tissues.

The instant specification teaches *in vivo* methods of determining profilin-1 expression on the surface of endothelial cells in the aorta, femoral, and carotid arteries of a subject, exemplified by the LDL receptor knockout (Ldlr) mouse (page 7, last paragraph). Example 1 teaches the determination of expression of profilin-1 in diabetic aortic tissue samples (page 17). Example 4 teaches determination of expression of profilin-1 in aortic sinus atherosclerotic plaques and disease-free adjacent areas (page 20). There is insufficient guidance and data in the specification to support Applicant's claims of correlating elevated levels of profilin-1 in non-rat/mouse/murine species with a suspected or actual disease or condition or state thereof. Without additional guidance, one of ordinary skill in the art would not be able to predictably make or use the claimed invention to determine whether elevated levels of profilin-1 in a non-rat/mouse/murine species are reasonably correlated with a suspected or actually disease or condition or state thereof.

There are no working examples or other data in the specification showing levels of profilin-1 in a generic human sample, aortic sample, or retinal sample. Although working examples are not required, they are helpful in determining whether Applicant has adequately taught how to make or use the invention, as claimed. Additionally, the teaching of Wittenmeyer et al., show the profilin-1 levels in humans to be highly regulated and tightly controlled on a tissue-by-tissue basis (page 1606, column 1, last paragraph to column 2, first paragraph). Moreover, there is no guidance in the specification as to how or why one of ordinary skill in the art should conduct an incredibly invasive procedure to obtain a sample human aortic or retinal tissue for profilin-1 expression levels. There is no guidance correlating the elevated level of profilin-1 expression with a vascular condition, a diabetic vascular condition, atherosclerosis, PVD, CVD, or a combination thereof based on determining profilin-1 expression levels in the human aorta or the human retina.

There is insufficient guidance and data in the specification to support Applicant's claims drawn to determining the level of profilin-1 in a sample of aortic tissue or retinal tissue from a non-rat/mouse/murine species and correlating the elevated level of profilin-1 expression with a vascular condition, a diabetic vascular condition, atherosclerosis, PVD, CVD, or a combination thereof. Without additional guidance, one of ordinary skill in the art would not be able to predictably make or use the claimed invention without undue experimentation to determine the level of profilin-1 in the aortic or retinal tissues of non-rat/mouse/murine species and correlating the elevated level of profilin-1 expression with a vascular condition, a diabetic vascular condition, atherosclerosis, PVD, CVD, or a combination thereof.

Due to the large quantity of experimentation necessary to determine the level of profilin-1 in a sample of aortic tissue or retinal tissue from a non-rat/mouse/murine species and correlate the elevated level of profilin-1 expression with a vascular condition, a diabetic vascular condition, atherosclerosis, PVD, CVD, or a combination thereof, the lack of direction/guidance presented in the specification regarding same, the absence of sufficient working examples directed to same, the complex nature of the invention, the state of the prior art establishing that different tissues express different levels of profilin-1 in different species, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 1, 6, and 9 are rejected under 35 U.S.C. 102(a) as being anticipated by Wittenmayer et al., (Mol Biol Cell 2004 Apr;15(4):1600-8. Epub 2004 Feb 6) (see also abstract of the Wittenmayer et al., for evidence of the Epub date) (both references previously cited of record).

Wittenmayer et al., teach a method of determining a disease state associated with endothelial cell dysfunction (tumor growth) *in vivo* in mice by determining the levels of profilin-1 (PFN-1) and relating elevated levels of PFN-1 to the state of the disease (tumor) (p. 1606, column 2, second paragraph; Figures 6 and 7) (compare instant claim1). Although it is known that profilin-1 normally acts as a tumor suppressor and low levels of expression of profilin-1 have been found in some tumor cells, Wittenmayer

et al., teach that elevation of overall profilin-1 levels in human breast carcinoma cells (endothelial cells) were capable of reverting the tumorgenic state (p. 1606, column 2, second paragraph).

Claim 1, as amended, in the "providing" step recites that a subject only need be "thought to be at risk" (in the alternative) of a condition (in the alternative) associated with endothelial cell dysfunction. All human beings are "thought to be at risk" for cardiovascular conditions and cancer, as cardiovascular conditions and cancer are the leading causes of death. The alternative reading of the "providing" step in claim 1 does not require the subject to have an actual or diagnosed disease. In its broadest reasonable interpretation, the claim also reads on determining the level of profilin-1 in a patient that is healthy or has elevated levels of profilin-1 in relation to a patient with a low profilin-1 expressing tumor, for example. Additionally, the "relating" step of claim 1 recites that an elevated level of profilin-1 relates to a disease or (in the alternative) a condition of the subject. In the broadest reasonable interpretation, the "reciting" step can be read to correlate an elevated level of profilin-1 with a condition of being healthy or a condition of not having a tumor. The alternative readings of claim 1, as amended, bring the claim within the anticipatory teachings of Wittenmayer et al.

It is noted that the specification defines the terms "elevated" and "increased" on page 4. However, the definition states that the term "generally refer to profilin-1 levels that exceed or are above those that would normally be expected in a subject that does no" have a predisposition for or does not suffer from a condition or disorder associated with EC dysfunction like, for example, DVD, atherosclerosis, or CVD." The "generalization" of the definition renders the definition lax and subject to additional interpretation. Additionally, because the claims recite "at a site" one of skill in the art would be taking relative measurements of profilin-1 levels depending on the "site" of interest (see, i.e. Wittenmayer et al., at page 1606, column 1, last paragraph to column 2, first paragraph; teaching that "PFN1 expression in most human tissues is within a narrow range, not exceeding a three-fold difference from the mean. Exceptions from this rule are spleen and tissues with a relatively high expression of other profiling isoforms, i.e. brain and testis.")

Wittenmayer et al., also teach determination of levels of profilin-1 in tissue samples, which contain vascular samples (Figures 6 and 7; especially the description of Figure 6) (compare instant claims 6 and 9).

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHERIE M. WOODWARD whose telephone number is (571)272-3329. The examiner can normally be reached on Monday - Friday 9:00am-5:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cherie M. Woodward/
Examiner, Art Unit 1647